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ELSEVIER SCIENCE FULL-TEXT ARTICLE

Modulation of the alpha 2 macroglobulin receptor/low density lipoprotein receptor related protein by interferon-gamma in human astroglial cells.

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Alpha 2 macroglobulin receptor/low density lipoprotein receptor-related protein (alpha 2 Mr/LRP) is a multi-functional cell surface receptor that has been implicated in important processes, such as atherogenesis, cellular migration, immune response and degenerative diseases. Its expression increases in human brain during Alzheimer's disease, tissue injury and neoplastic transformation. In the present paper we studied the regulation of alpha 2 Mr expression by interferon-gamma (IFN gamma) in human astrocytoma cell lines and in fetal astrocytes. Western blots demonstrated an increase of the alpha 2 Mr expression after 24 h of IFN gamma treatment. This effect paralleled the up-regulation of alpha 2 Mr mRNA, as detected by PCR. By prolonging incubation with IFN gamma, we observed a decrement of alpha 2 Mr in IFN gamma treated cells, both by western blot and cytometric analysis. Since in the same cells IFN gamma also up-regulates alpha 2 macroglobulin, this effect may be due to an augmented degradation of the receptor during its recycling.

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Ligand interaction of human alpha 2-macroglobulin-alpha 2-macroglobulin receptor studied by partitioning in aqueous two-phase systems.

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Alpha 2-macroglobulin (alpha 2-M) is a major proteinase inhibitor in human blood and tissue. Besides its antiproteolytic potential, alpha 2-M was found to modulate antigen- and mitogen-driven immune responses and cell growth by binding and transporting distinct cytokines, growth factors and hormones. The inhibitor is cleared from circulation by binding to a multifunctional cellular receptor present on different cell types. Alpha 2-M, as well as its receptor, are capable of binding a variety of ligands. In the present study we have applied aqueous two-phase systems to analyze the interaction of IL-1 beta and alpha 2-M receptor to different forms of alpha 2-M. The partition of IL-1 beta was changed by addition of transformed alpha 2-M to the two-phase systems rather than by the native inhibitor. The interaction between IL-1 beta and alpha 2-M was enhanced by divalent cations. In addition, the complex formation between 125I-labelled receptor and alpha 2-M could clearly be demonstrated by partitioning. In the presence of divalent cations, transformed alpha 2-M, in contrast to the native inhibitor, effectively changed the partition of the receptor. However, the observed alteration of the partition coefficient was found to be less compared with the values obtained by partitioning of the receptor in the presence of whole plasma containing the inhibitor in equivalent concentrations. The results indicate that other components of the plasma exist which competitively bind to the receptor but independent of Ca2+-ions.

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1: J Immunol 1993 Jan 1;150(1):48-58

Receptor-mediated antigen delivery into macrophages. Complexing antigen to alpha 2-macroglobulin enhances presentation to T cells.

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Macrophages secrete alpha 2-macroglobulin (alpha 2M), a protein that may facilitate early Ag handling. alpha 2M is able to entrap and form covalent linkages with diverse proteins during a transient proteinase-activated state. The resulting complexes are rapidly endocytosed after binding to high affinity receptors. Such a system could be capable of efficiently delivering a multitude of proteins to macrophages. We have used T hybridoma clones that respond only to hen egg lysozyme, in a MHC-restricted manner, to probe the effect of complex formation on Ag uptake and processing by murine macrophages. Radiolabeled lysozyme was internalized more rapidly and to a greater extent when bound to alpha 2M than when unbound. Macrophages pulsed with lysozyme-alpha 2M-elastase complexes required 200 to 250 times less Ag than those pulsed with free lysozyme to achieve effective presentation to T cells. Adding equimolar amounts of alpha 2M-elastase complexes, or of alpha 2M-methylamine, to free lysozyme had no effect on basal lysozyme presentation. Receptor-recognized forms of alpha 2M, but not lysozyme or BSA, competed effectively for both uptake and presentation of lysozyme-alpha 2M-elastase complexes. These results indicate that proteinase-activated alpha 2M can enhance Ag processing by carrying Ag into macrophages through a receptor-mediated process.

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ELSEVIER SCIENCE FULL-TEXT ARTICLE

Stress proteins and the immune response.

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The heat shock or stress response is one of the most highly conserved adaptive responses in nature. In single cell organisms, the stress response confers tolerance to a variety of stresses including hyperthermia, hyperoxia, hypoxia, and other perturbations, which alter protein synthesis. This tolerance phenomenon is also extremely important in the multicellular organism, resulting in not only thermal tolerance, but also resistance to stresses of the whole organism such as ischemia-reperfusion injury. Moreover, recent data indicates that these stress proteins have the ability to modulate the cellular immune response.Although the terms heat shock proteins (HSPs) and stress proteins are often used interchangeably, the term stress proteins includes the HSPs, the glucose-regulated proteins (GRPs) and ubiquitin. The stress proteins may be grouped by molecular weight ranging from the large 110 kDa HSP110 to ubiquitin at 8 kDa. These proteins serve as cellular chaperones, participating in protein synthesis and transport through the various cellular compartments. Because these proteins have unique cellular localizations, the chaperone function of the stress proteins often involves a transfer of peptides between stress proteins as the peptide is moved between cellular compartments. For example, HSP70 is a cytosolic and nuclear chaperone, which is critical for the transfer of cellular peptides in the mitochondrion through a hand-off that involves mitochondrial HSP60 at the inner mitochondrial membrane. Similarly, cytosolic proteins are transferred from HSP70 to gp96 as they move into the endoplasmic reticulum.The central role of the stress proteins in the transfer of peptides through the cell may be responsible for the recently recognized importance of the stress proteins in the modulation of the immune system [Feder, M.E., Hofmann, G.E., 1999. Heat-shock proteins, molecular chaperones, and the stress response: evolutionary and ecological physiology. Annu. Rev. Physiol. 61, 243-282.]. This importance in immune regulation is best

addressed using Matzinger's model of the immune response - The Danger Theory of Immunity [Matzinger, P., Fuchs, E.J., 1996. Beyond self and non-self: immunity is a conversation, not a war. J. NIH Res. 8, 35-39.]. Matzinger suggests that an immune system model based on the differentiation between "self and non-self" does not easily account for the changes that occur in the organism with growth and development. Why, for example does an organism not self-destruct when the immune system encounters the myriad of new peptides generated at puberty? Instead, she proposes a model of immune function based on the ability to detect and address dangers. This model states that the basic function of all cells of the organism is appropriately timed death "from natural causes". This type of cell death, or apoptosis, generates no stress signals. If, on the other hand, a cell is "murdered" by an infectious agent or dies an untimely death due to necrosis or ischemia, the cell undergoes a stress response with the liberation of stress protein-peptide complexes into the extracellular environment upon cell lysis. Not only do they serve as a "danger signal" to alert the immune system to the death of a cell under stress, but their role as protein carriers allows the immune effector cells to survey the peptides released by this stressed cell and to activate against new or unrecognized peptides carried by the stress protein. Matzinger bases the Danger Theory of Immunity on three "Laws of Lymphotics". These laws state that: (1) resting T lymphocytes require both antigen stimulation by an antigen-presenting cell (APC) and co-stimulation with a danger signal to become activated; (2) the co-stimulatory signal must be received through the APC; and (3) T cells receiving only antigen stimulation without the co-stimulatory signal undergo apoptosis. The Danger Theory gives a simple model for both tolerance and activation. (ABSTRACT TRUNCATED)

Publication Types:

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